Organic Process Research & Development **2000**, *4,* 505–508

Aerobic Oxidation of Methylpyridines to Pyridinecarboxylic Acids Catalyzed by *N*-Hydroxyphthalimide

Akihiro Shibamoto, Satoshi Sakaguchi, and Yasutaka Ishii*

Department of Applied Chemistry, Faculty of Engineering & High Technology Research Center, Kansai University, Suita, Osaka 564-8680, Japan

Abstract:

Selective aerobic oxidation of methylpyridines to pyridinecarboxylic acids was successfully achieved by the use of a radical catalyst, *N*-hydroxyphthalimide (NHPI), in the presence of Co(II) and/or Mn(II) salts. The oxidation of 3-methylpyridine by NHPI combined with $Co(OAc)_2$ under O_2 (1 atm) in AcOH at 100 °C gave 3-pyridinecarboxylic acid (76%). The reaction was found to be enhanced by addition of a small amount of $Mn(OAc)_2$ to the catalytic system. The reaction with 20 atm of air, catalyzed by NHPI−$Co(OAc)_2$−$Mn(OAc)_2$ at 150 °C for 1 h, gave 3-pyridinecarboxylic acid (85%). 4-Methylpyridine was much less easily oxidized than 3-methylpyridine. The co-oxidation of 3-methylpyridine and 4-methylpyridine by NHPI−$Co(OAc)_2$−$Mn(OAc)_2$ at 150 °C for 5 h gave results that were better than those obtained from individual oxidations, forming 3-pyridinecarboxylic acid (93%) and 4-pyridinecarboxylic acid (70%). The NHPI-catalyzed oxidation of methylpyridines would provide an attractive direct method which has long been desired in the chemical industry for the manufacturing of pyridinecarboxylic acids.

Introduction

Pyridinecarboxylic acids derived from methylpyridines are important intermediates as pharmaceutical materials. In particular, 3-pyridinecarboxylic acid, which is used as a precursor of vitamin B_3, has been manufactured in large scale.[1] Two basic methods are employed for the synthesis of pyridinecarboxylic acids: one method is based on the hydrolysis of pyridinecarboxamides derived from pyridinecarbonitriles, and the other is the oxidation of alkylpyridines by air, nitric acid, selenium dioxide, etc.[2] The ammoxidation of methylpyridines forms pyridinecarbonitriles, which are subsequently hydrolyzed to pyridinecarboxylic acids through pyridinecarboxamides.[3] 3-Pyridinecarboxylic acid has been commercially manufactured by nitric acid oxidation of 5-ethyl-2-methylpyridine.[2a]

Aerobic oxidation of methylpyridines is thought to be a straightforward approach to pyridinecarboxylic acids and to provide a practical method from the environmental and economic viewpoints. However, there has been little information on the aerobic oxidation of these substrates so far.[4−6] According to the patent literature, these oxidations occur under severe reaction conditions in the presence of cobalt and manganese ions with highly corrosive promoters such as bromide salts.[5] Recently, the autoxidation of methylpyridines has been reported to be accelerated by the addition of lithium chloride as the promoter.[5b] It is very important to carry out the aerobic oxidation without any corrosive halide ions as promoters, since the oxidation in the absence of halide ions did not call for the employment of a reactor made of titanium alloy.[6] Therefore, it is very attractive to develop an efficient catalytic method for the production of pyridinecarboxylic acids from methylpyridines by aerobic oxidation under mild conditions.

In recent years, we have developed a novel catalytic aerobic oxidation system of a variety of hydrocarbons using *N*-hydroxyphthalimide (NHPI) as the key catalyst.[7] Thus, alkanes such as isobutane, cyclohexane, and toluene could be efficiently oxidized with molecular oxygen by NHPI combined with $Co(OAc)_2$ under mild conditions to give oxygen-containing compounds such as alcohols, ketones, and carboxylic acids.[8] In this paper, we report the NHPI-catalyzed aerobic oxidation of methylpyridines, which are difficult to selectively oxidize by conventional autoxidation.

Results and Discussion

1. Oxidation of 3-Methylpyridine. Representative results for the oxidation of 3-methylpyridine (**1**) with molecular oxygen (1 atm) catalyzed by NHPI combined with a small amount of a transition metal ion in acetic acid at 100 °C are given in Table 1.

---

(1) Davis, D. D. In *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Gerhartz, W. Ed.; VCH: Weinheim, 1985; Vol. A27, p 587.

(2) Davis, D. D. In *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Gerhartz, W. Ed.; VCH: Weinheim, 1985; Vol. A27, p 584 (b) Steckhan, E.; Azzem, M, A. *Heterocycles* **1990**, *31*, 1959. (c) Teubner, H.; Schmidt, M.; Teubner, H.; Tiyze, H.; Schmind, M.; Schick, H. *Chem. Abstr*. **1988**, *108*, 150322. (d) Paraskewas, P. *Synthesis* **1974**, *11*, 819. (e) Beletskaya, I. P.; Grinfel'd, A. A.; Artamkina, G. A. *Tetrahedron Lett*. **1984**, *25*, 4989. (f) Mukhopadhyay, S.; Chandalia, S. B. *Org. Process Res. Dev*. **1999**, *3*, 455.

(3) Beschke, H.; Friedrich, H.; Mueller, K. P.; Schreyer, G. *Chem. Abstr*. **1977**, *86*, 43576. (b) Gaddis, J. L.; Spencer, H. G. *Chem. Abstr*. **1980**, *93*, 79696.

(4) Hoelderich, W. F. *Appl. Catal. A*: *General*, **2000**, *194−195*, 487.

(5) Roy, A. N.; Guha, D. K.; Bhattacharyya, D. *Indian Chem. Eng*. **1982**, *24*, 46 and references therein. (b) Mukhopadhyay, S.; Chandalia. S. B. *Org. Process Res. Dev*. **1999**, *3*, 227. (c) Hashimoto, T.; Nakamura, K.; Takagawa, M. Jpn Kokai Tokkyo 92, 02, 772, 1997; *Chem. Abstr*. **1997**, *127*, 176350.

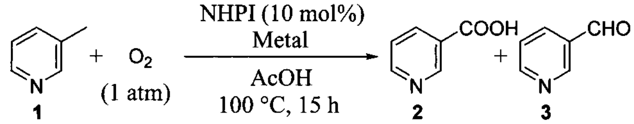
(6) Inoue, H. T. Jpn. Kokai 76, 29, 483, 1976; *Chem. Abstr*. **1976**, *85*, 94233.

(7) Ishi, Y.; Nakayama, K.; Takeno, M.; Sakaguti, S.; Iwahama, T.; Nisiyama, Y. *J. Org. Chem*. **1995**, *60*, 3934.

(8) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama. *J. Org. Chem*. **1996**, *61*, 4520. (b) Iwahama, T.; Shoujo, K.; Sakaguchi, S.; Ishii, Y. *Org. Process Res. Dev*. **1998**, *2*, 255. (c) Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett*. **1995**, *38*, 6923. (d) Ishii, Y.; Kato, S.; Iwahama, T.; Sakaguchi, S. *Tetrahedron Lett*. **1996**, *37*, 4993. (e) Sakaguchi, S.; Kato, S.; Iwahama, T.; Ishii, Y. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 1237. (f) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi., S.; Ishii, Y. *J. Org. Chem*. **1997**, *62*, 6810.

10.1021/op000061h CCC: $19.00

Table 1. **Effect of transition metal salt on aerobic oxidation of 3-methylpyridine (1) by NHPI**[a]



run	metal	conv (%)	yield (%) 2	yield (%) 3
1		no reaction		
2	$Co(acac)_2$	60	53	1
3	$Co(acac)_2$	46	43	1
4	$Mn(OAc)_2$	3	trace	
5	$Cu(OAc)_2$	5	2	
6	$VO(acac)_2$	2		
7	$Fe(acac)_3$	8	1	
8	$Ni(OAc)_2$	3		

[a] **1** (2 mmol) was allowed to react with O_2 (1atm) in the presence of NHPI (10 mol %) and a transition metal (0.5 mol %) in acetic acid (7 mL) at 100 °C for 15 h.

Table 2. **Effect of quantity of $Co(OAc)_2$ on aerobic oxidation of 1 by NHPI**[a]

run	$Co(OAc)_2$ (mol %)	conv (%)	yield (%) 2	yield (%) 3
1	0.1	5	4	<1
2	0.5	60	53	1
3	1.0	67	63	1
4	1.5	82	76	1
5	2.0	87	77	1

[a] **1** (2 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %) and $Co(OAc)_2$ in acetic acid (7 mL) at 100 °C for 15 h.

Table 3. **Effect of $Mn(OAc)_2$ on aerobic oxidation of 1 by NHPI−$Co(OAc)_2$**[a]

run	$Co(OAc)_2$ (mol %)	$Mn(OAc)_2$ (mol %)	conv (%)	yield (%) 2	yield (%) 3
1	1.5		82	76	2
2	1.5	0.1	80	74	1
3	1.0		67	63	1
4	1.0	0.1	77	72 (70)[c]	1
5	0.5		60	53	1
6	0.5	0.1	78	73	1
7	0.1		5	4	
8	0.1	0.1	48	41	1
9	0.1	0.5	72	65	2
10[b]	0.5	0.1	65	62 (57)[c]	2

[a] **1** (2 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %), $Co(OAc)_2$, and $Mn(OAc)_2$ in acetic acid (7 mL) at 100 °C for 15 h. [b] The reaction was carried out using **1** (10 mmol) in acetic acid (35 mL). [c] Isolated yield.

The oxidation of **1** in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (0.5 mol %) produced 3-pyridinecarboxylic acid (**2**), along with a small amount of 3-pyridinecarboaldehyde (**3**). However, the oxidation of **1** in the absence of $Co(OAc)_2$ under these conditions did not lead to any oxidation products at all. Although $Co(acac)_2$ was also effective for the oxidation of **1** (run 3), transition metal salts other than Co salts did not accelerate the oxidation of **1** (runs 4−8). In a previous paper, we revealed the role of a Co(II) ion in the NHPI-catalyzed oxidation of alkanes with molecular oxygen and showed that the Co(II) species reacts with dioxygen to generate a cobalt−oxygen complex, such as $L_2CoOO^\bullet$ and $L_2CoOOCoL_2$, which assist the abstraction of the hydrogen atom from the hydroxyimide group in the NHPI to form phthalimide *N*-oxyl (PINO) radical.[8f,9]

The effect of the quantity of $Co(OAc)_2$ on the present oxidation of **1** with O_2 by NHPI was examined (Table 2).

The yield of **2** increased as the quantity of the $Co(OAc)_2$ added to the NHPI was increased. The oxidation of **1** by addition of 1.5 mol % of $Co(OAc)_2$ to the NHPI (10 mol %) afforded **2** in satisfactory yield (76%) at 82% conversion of **1**. To our best knowledge, this is the first successful oxidation of **1** to **2** by O_2 (1 atm) under the mildest conditions among the aerobic oxidations examined earlier. The oxidation of **1** by the addition of $Co(OAc)_2$ (2 mol %) to the NHPI (10 mol %) gave almost the same result as that obtained for the addition of the 1.5 mol % of $Co(OAc)_2$.

It has long been known that a combined system of Co and Mn ions is effective for the autoxidation of hydrocarbons.[10] Thus, the influence of the Mn ion on the oxidation of **1** by the NHPI−$Co(OAc)_2$ was examined (Table 3).

There was slight effect of $Mn(OAc)_2$ on the oxidation of **1** by the NHPI (10 mol %)−$Co(OAc)_2$ (1.5 mol %) system (runs 1 and 2), but a remarkable enhancement was observed when $Mn(OAc)_2$ was added to the NHPI (10 mol %)−$Co(OAc)_2$ (0.1−0.5 mol %) systems (runs 6 and 8). Interestingly, the addition of 0.5 mol % of $Mn(OAc)_2$ to the NHPI (10 mol %)−$Co(OAc)_2$ (0.1 mol %) system gave **2** in 65% yield at 72% conversion of **1** (run 9). A larger-scale experiment was also run. The oxidation of 10 mmol of **2** under the same reaction conditions as those used for run 6 gave **2** in 62% yield (run 10).

It is very important to utilize air instead of dioxygen in industrial processes. Thus, the oxidation of **1** by NHPI (10 mol %)−$Co(OAc)_2$ (0.5 mol %)−$Mn(OAc)_2$ (0.1 mol %) under 20 atm of air in several solvents at varying reaction temperatures was examined (Table 4).

The oxidation of **1** in acetic acid at 150 °C for 5 h afforded **2** in 89% yield (91% conversion). Almost the same result was obtained in the oxidation at 140 °C, but the yield of **2** decreased to 69% (73% conversion) when the reaction temperature was lowered to 120 °C. **2** was obtained in 77% yield (81% conversion) in the oxidation, even at 100 °C, although the reaction must be prolonged to 15 h (run 5). Oxidation was difficult at 80 °C. Among the solvents examined, acetic acid was the best. Reactions in benzonitrile and in acetonitrile afforded **2** in moderate yields, 42% and 40%, respectively (runs 8 and 9). However, the addition of a small amount of acetic acid to the reaction system led to a slightly higher yield of **2** (run 10).

---

(9) Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493.

(10) Shigeyasu, T.; Kurokawa, A.; Ozaki, S. *Nippon Kagaku Kaishi* **1985**, *2*, 207. (b) Kamiya, Y.; Nakajima, T.; Sakoda, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2211. (c) Kamiya, Y.; Kotake, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2780.

Table 4. **Oxidation of 1 with air by NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ catalyst at varying temperatures**[a]

run	solvent	temp (°C)	conv (%)	yield (%) 2	yield (%) 3
1	AcOH	150	91	89	
2	AcOH	140	90	86	trace
3	AcOH	120	73	69	1
4	AcOH	100	40	35	1
5[b]	AcOH	100	81	77	1
6[b,c]	AcOH	100	66	60	1
7	AcOH	80	10	8	trace
8	PhCN	150	45	42	1
9	MeCN	150	53	40	1
10[d]	MeCN	150	60	50	2

[a] **1** (2 mmol) was allowed to react with 20 atm of air in the presence of NHPI (10 mol %), Co(OAc)$_2$ (0.5 mol %), and Mn(OAc)$_2$ (0.1 mol %) at 150 °C in solvent (7 mL) for 5 h. [b] The reaction was carried out for 15 h. [c] The reaction was carried out with 5 atm of air. [d] AcOH (2 mmol) was added.

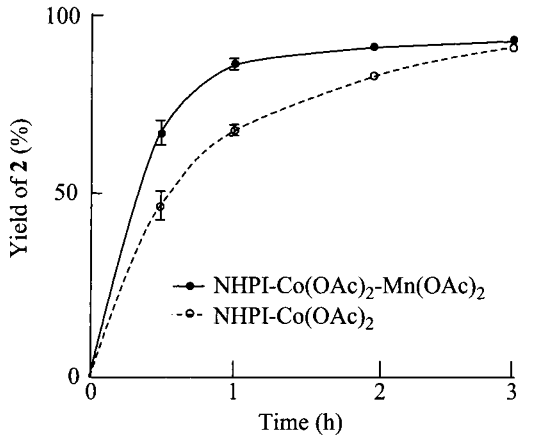


Figure 1. **Time dependence curves for the oxiation of 1 to 2 under 20 atm of air by NHPI (10 mol %)−Co(OAc)$_2$ (0.5 mol %) or NHPI (10 mol %)−Co(OAc)$_2$ (0.5 mol %)−Mn(OAc)$_2$ (0.1 mol %) in AcOH (7 mL) at 150 °C.**

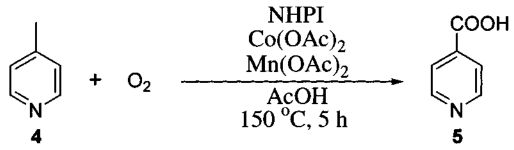
Figure 1 shows the time dependence curves for the oxidation of **1** to **2** under 20 atm of air by both NHPI−Co(OAc)$_2$ and NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ systems at 150 °C.

This indicates that the oxidation of **1** by the NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ system took place very fast and was complete within about 1 h. On the other hand, the time taken to complete the oxidation by the NHPI−Co(OAc)$_2$ system was about 3 h. Unfortunately, the effect of the Mn ion on the rate enhancement in this oxidation is difficult to explain at the present time.

2. Oxidation of 4-Methylpyridine. Table 5 shows the results of oxidation of 4-methylpyridine (**4**) under 20 atm of air by the NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ system under various conditions.

In contrast to the oxidation of **1** by the NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ system, where **2** was formed in good yield (89%) (Table 4, run 1), 4-methylpyridine **4** was oxidized with some difficulty under these conditions to form 4-pyridinecarboxylic acid (**5**) in moderate yield (22%) (run 1). However, the same oxidation by the NHPI−Co(OAc)$_2$ system in the absence of Mn(OAc)$_2$ led to **5** in only 2% yield (run 2).

Table 5. **Oxidation of 4-methylpyridine (4) with air by NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ catalyst under various conditions**[a]



run	NHPI (mol %)	Co(Ac)$_2$ (mol %)	Mn(OAc)$_2$ (mol %)	conv (%)	yield (%), 5
1	10	0.5	0.1	25	22
2	10	0.5		3	2
3	10		0.5	no reaction	
4	10	1	0.5	46	44
5	10	1	1	52	46
6[b]	10	0.5	1	15	10
7	15	1	1	62	56
8	20	1	1	67	60
9[c]	10	1	0.5	18	15
10[c,d]	10	1	0.5	43	39

[a] **4** (2 mmol) was allowed to react with 20 atm of air in the presence of NHPI, Co(OAc)$_2$, and Mn(OAc)$_2$ in AcOH (7 mL) at 150 °C for 5 h. [b] The reaction was carried out at 120 °C. [c] The reaction was carried out in MeCN (7 mL). [d] AcOH (2 mmol) was added.

Table 6. **Co-oxidation of 3-methylpyridine (1) and 4-methylpyridine (4) with air by NHPI−Co(OAc)$_2$−Mn(OAc)$_2$ catalyst**[a]

run	1 (mmol)	4 (mmol)	conv (%) 1	conv (%) 4	yield (%) 2	yield (%) 5
1	1	1	95	75	93	70
2	0.67	1.33	89	61	87	56
3	1.33	0.67	90	61	88	58
4[b]	1	1	45	15	43	13
5[c]	1	1	75	41	72	38

[a] A mixture of **1** and **4** was allowed to react with 20 atm of air in the presence of NHPI (10 mol %), Co(OAc)$_2$ (0.5 mol %), and Mn(OAc)$_2$ (0.1 mol %) in AcOH (7 mL) at 150 °C for 5 h. [b] The reaction was carried out at 120 °C. [c] The reaction was carried out in the absence of Mn(OAc)$_2$.

When the NHPI (10 mol %)−Co(OAc)$_2$ (1.0 mol %)−Mn(OAc)$_2$ (1 mol %) system was employed as the catalyst, **5** was obtained in 46% yield at 52% conversion (run 5). Oxidation using 20 mol % of NHPI under these conditions afforded **5** in 60% yield (67% conversion). Oxidation of **4** using acetonitrile as a solvent resulted in low conversion (18%) (run 9). However, it is interesting to note that the addition of a small amount of acetic acid to the reaction system led to considerable improvements in the conversion of **4** and the yield of **5** (run 10).

To promote the oxidation of **4**, the co-oxidation of **4** and **1** was carried out under several reaction conditions (Table 6).

The co-oxidation of **1** and **4** gave results that were better than those obtained from the individual oxidations of **1** and **4**. For instance, a 1:1 mixture of **1** and **4**, oxidized under 20 atm of air by the same catalytic system that was employed for the oxidation of **1** (run 1 in Table 5) at 150 °C for 5 h, gave **2** and **5** in 93% and 70% yields, respectively (run 1). The co-oxidation of a 1:2 mixture of **1** and **4** afforded **2**

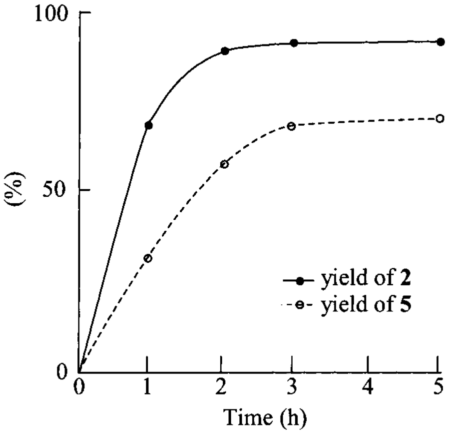


Figure 2. **Time dependence curves for the oxiation of a 1:1 mixture of 1 and 4 with 20 atm of air in AcOH (7 mL) by NHPI (10 mol %)−CO(OAc)$_2$ (0.5 mol %)−Mn(OAc)$_2$ (0.1 mol %) at 150 °C.**

(87%) and **5** (56%) (run 2). The result of the oxidation of a 2:1 mixture of **1** and **4** was almost the same as that of the oxidation of the 1:2 mixture (run 3). The co-oxidation of **1** and **4** at 120 °C led to **2** (43%) and **5** (13%) (run 4). As shown in run 2 in Table 5, it was difficult to oxidize **4** by the NHPI−Co(OAc)$_2$ in the absence of Mn(OAc)$_2$, but, in the co-oxidation of **1** and **4**, **4** was oxidized by the NHPI−Co(OAc)$_2$ system to give **5** in 38% yield (run 5).

From the time dependence of the co-oxidation of **1** and **4** (Figure 2), it was found that the oxidation of **1** to **2** was complete in 2 h, but the oxidation of **4** proceeded much more slowly than that of **1** and was terminated at about 70% yield.

The oxidation of **4** was considerably accelerated in the presence of **1**. This shows that radical intermediates such as 3-ArCH$_2$OO$^•$ and 3-ArCH$_2$O$^•$ (where Ar is a pyridinyl moiety) generated from **1** serve as chain-transfer agents to facilitate the generation of a radical species such as 4-ArCH$_2^•$ from **4**. Therefore, when **1** was consumed in the co-oxidation of **1** and **4**, the oxidation of **4** did not proceed easily, as shown in Figure 2.

In summary, we have found an effective catalytic method for the direct aerobic oxidation of methylpyridines to pyridinecarboxylic acids. Further elaboration of this method would provide a direct route to pyridinecarboxylic acids from methylpyridines.

Experimental Section

General. The starting materials, 3- and 4-methylpyridines (**1** and **4**), and catalysts were commercially available and used without purification. GC analysis was performed with a flame ionization detector using a 0.2-mm × 30-m capillary column (OV-17). LC was performed with a UV detector (254 nm) using a 4.6-mm × 270-mm column chromatography (Mightysil RP-18, Kanto Chem. Co Ltd). ^{1}H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, in DMSO-d_6 with Me$_4$Si as the internal standard. Infrared (IR) spectra were measured using NaCl or KBr pellets. GC−MS spectra were obtained at an ionization energy of 70 eV. The yields of products were estimated from the peak areas on the basis of the internal standard technique by the use of GC or LC.

A Typical Procedure for the Oxidation of 3-Methylpyridine (1) or 4-Methylpyridine (4) under O$_2$ (1 atm). To a solution of NHPI (10 mol %) and transition metals in acetic acid (7 mL) in a pear-shaped flask was added **1** or **4** (2 mmol). The flask was equipped with a balloon filled with O$_2$ (1 atm). The mixture was stirred at 100 °C for 15 h. After the reaction, the solvent was removed under reduced pressure to afford a brown solid. To remove NHPI, metal salts, and side products, the resulting solids obtained by the oxidation of **1** or **4** were dissolved in a small amount of methanol or DMSO, respectively, and the solution was refluxed. The solution was cooled in an ice bath, and excess acetonitrile was added to give a pure white solid, 3-pyridinecarboxylic acid (**2**) or 4-pyridinecarboxylic acid (**5**).

All products were identified by comparison of their spectral data with those of authentic samples.

A Typical Procedure for the Oxidation of 1 or 4 under Air (20 atm). **1** or **4** (2 mmol), NHPI (10 mol %), Co(OAc)$_2$ (0.5 mol %), and Mn(OAc)$_2$ (0.1 mol %) in AcOH (7 mL) were placed in a 50-mL Teflon-coated autoclave, and 20 atm of air was charged. The workup was performed by the procedure described above.

Acknowledgment

This work was partly supported by Research for the Future program JSPS.

Received for review June 7, 2000.

OP000061H